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Research Article

CELL PROLIFERATION AND DIFFUSION MAY PLAY IMPORTANT ROLE DETERMINING THE TYPE OF GENE THERAPY IN CASE OF BRAIN TUMOR BY USING TRANSITION POINT IN A 3D QUANTITATIVE TUMOR GROWTH MODEL

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Abstract

Gene therapy is a type of specialized treatment using genes to treat illnesses. Researchers have been developing different types of gene therapy to treat cancer. It is still at research level. Some of these treatments are being looked at in clinical trials.

Some people inherit faulty genes that increase their risk of developing particular types of cancer. Genetic testing is available for some of these faulty genes. Genetic testing can also find some of the inherited faulty genes that increase cancer risk. Transition point is a promising characteristic that is observed in a 3D quantitative brain tumor growth model based on cell proliferation and diffusion. Transition point can play an important role in the treatment plan by gene therapy. The tumor diffuses more rapidly than the cell proliferates for a short period of time followed by an exponential growth in detectable tumor size while its growth is observed at different time points across a one year time frame with different values for proliferation/diffusion (ρ/D).This growth pattern results in a transition point in the voxel-wise cell count with respect to time when the rate of diffusion and proliferation equilibrate and in some cases result undetectable tumor for a period of time. A person may go for a regular medical check-up with gene testing. If testing shows that he or she has a faulty gene (inherited in some cases), the physician may suggest him or her to go for further clinical check up by MRI or CT scan or

PET-CT scan. The 3D model and its corresponding transition point may help to investigate the ratio of growth rate to the diffusion coefficient (ρ/D) which determines the portion of tumor that is detectable. It may help the doctors to focus on tumor phase, whether it has crossed the transition point in its life span or not and thus decide the treatment plan by gene therapy for the patient accordingly.

Key Words: Tumor growth model, Diffusion, Proliferation, Transition point, Gene therapy.

Background study on genes and cells

Genes are coded messages that tell cells how to make proteins. Proteins are the molecules that control the way cells behave. Our genes decide what we look like and how our body works. We have many thousands of separate genes. Genes are made of DNA (deoxyribonucleic acid) and they are in the nucleus of the cell. Cancer cells are different from normal cells having mutational properties in cell division and tumor formation. Genetic mutation may play role to make the normal cell into a cancerous one influenced by environmental or lifestyle factors. A group of people inherit faulty genes that increase their risk of particular types of cancer. Inherited **genetic** mutations play a major role in about 5 to 10 **percent** of all **cancers**. [1] Advances in understanding and manipulating genes have set the stage for scientists to modify a person's genetic material to fight or prevent disease. Gene therapy is an experimental treatment that involves introducing genetic material (DNA or RNA) into a person's cells to fight disease. Gene therapy is being studied in clinical trials (research studies with people) for many different types of cancer and for other diseases. [2] Getting genes into cancer cells is one of the most difficult aspects of gene therapy. Researchers are working on finding new and better ways of doing this. The gene is usually taken up by or into the cancer cell by a carrier called a vector. The most common types of carrier used in gene therapy are viruses because they can enter cells and deliver genetic material. Some viruses have been changed in the laboratory so that they target cancer cells and not healthy cells. So they only carry the gene into cancer cells. [1] The ideas for new treatment plans by gene therapy have come about because we are beginning to understand how cancer cells are different from normal cells by expression. [1] All cancers begin in cells. Our bodies are made up of more than a hundred million (100,000,000,000,000) cells. Cancer starts with changes in one cell or a small group of cells. Usually, we have just the right number of each type of cell. This is because cells produce signals to control how much and how often the cells divide. If any of these signals are faulty or missing, cells may start to grow and

multiply too much and form a lump called a tumor. A primary tumor is where the cancer starts. For a cancer to start, certain changes take place within the genes of a cell or a group of cells. Different types of cells in the body do different jobs, but they are basically similar. They all have a control centre called a nucleus. Inside the nucleus are chromosomes made up of thousands of genes. Genes contain long strings of DNA (deoxyribonucleic acid), which are coded messages that determine the cell how to behave or act. [3]

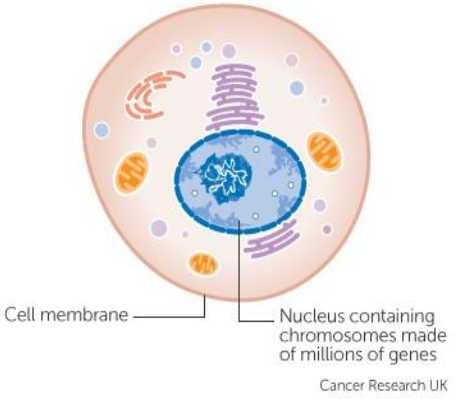


Figure 1: Internal structure of a normal cell [3].

Each gene is an instruction that tells the cell to make something. This could be a protein or a different type of molecule called RNA. Together, proteins and RNA control the cell. They decide the nature of growth and reproduction, division or death of a cell in an orderly and controlled way. They make sure that all the cells produced are needed to keep the body healthy. Sometimes a change happens in the genes when a cell divides. This is a mutation. It means that a gene has been damaged or lost or copied twice. Mutations can happen by chance when a cell is dividing. Some mutations mean that the cell no longer understands its instructions and starts to grow out of control. There have to be about half a dozen different mutations before a normal cell turns into a cancer cell. Mutations in particular genes may mean that a cell starts producing too many proteins that trigger a cell to divide. Or it stops producing proteins that normally tell a cell to stop dividing. Abnormal proteins may be produced that work differently to normal. Mutations can happen by chance during cell division. They can also be caused by the processes of life inside the cell or by things coming from outside the body, such as the chemicals in tobacco smoke. And some people can inherit faults in particular genes that make them more likely to develop a cancer. It can take many years for a damaged cell to divide and grow and form a tumor big enough to cause symptoms or show up on a scan. [3] Mathematical model can help the prognosis to decide the treatment plan.

Analysis of mathematical model

Glioma are major intracranial tumors that constitute more than 50% of all primary brain tumors and are one of the major causes of morbidity and mortality in the world. One of the fundamental problems in

treating glioma is their highly diffusive and infiltrative nature that makes it difficult to differentiate between healthy brain tissue and the tumor boundary as seen in various conventional imaging modalities.

The 3D mathematical model of tumor growth by Sohana Tanzeem et al. [4][5] focuses on developing a 3D mapping of brain tumor (glioma) growth based on cell proliferation and diffusion which provides a more sensitive method to better delineate tumor growth patterns by focusing on the extent of tumor invasiveness. This model incorporates actual tissue mapping of white and gray matter from a pediatric patient treated for acute lymphoblastic leukaemia at St. Jude Children's Research Hospital, Memphis, Tennessee, USA. Diffusion and proliferation rates were chosen to model both high grade and low grade glioma and tested for seed points arising from both white matter and gray matter. The tumor seed was assumed to be a Gaussian distribution with a mean of zero and a standard deviation of one (measured in millimetres).

Original works from Burgess et al. [6] Cruywagen et al. [7], Tracqui et al. [8] and Woodward et al. [9] develop a mathematical model of glioma growth based solely on cell proliferation and diffusion.

$$\frac{dc}{dt} = \nabla.(D\nabla c) + \rho c$$

where $c(x,t)$ is the number of cells, ρ (1/day) represents the net rate of growth of cells including proliferation and death (or loss), D (mm^2/day) is the diffusion coefficient of cells in brain tissue and ∇ represents the spatial gradient.

The diffusion term describes the active migration of the glioma cells using a simple Fickian diffusion where cells move from regions of higher to lower densities.

Sohana Tanzeem et al. [4][5] proposed to solve equation (1) through equations (2) and (3).

$$\frac{dc}{dt} = D\nabla^2 c + \rho c \qquad (2)$$

$$c = T(t)R(x,y,z) \qquad (3)$$

The 3D model developed by Sohana Tanzeem et al. is as follows.

$$c(x,y,z,t) = c_0 \frac{1}{\Pi^{3/2} G^3} . e^{-\frac{x^2+y^2+z^2}{G^2}} . e^{\rho t} \qquad (4)$$

where c_0 is the initial number of cells and

$$G^2 = a^2\left(1+\frac{4Dt}{a^2}\right) \qquad (5)$$

where a is the standard deviation for the seed point.

By differentiating number of cells with respect to time, the following expression for transition point was obtained by Sohana Tanzeem et al. :

$t = \frac{1}{4D}\left(\frac{6D}{\rho} - a^2\right)$. Here, $D = D_w$ when the seed is in white matter and $D = D_g$ when seed is in gray matter.

Results

Sohana Tanzeem et al. [4][5] investigated the performance of this model under several experimental conditions. Diffusion and proliferation rates were chosen to model both high grade and low grade glioma and tested for seed points arising from both white matter or gray matter.

A 1 mm^3 Gaussian seed voxel was initialized in white matter of a segmented image and the growth of tumor (both high and low grade) was observed in serial time steps from three orthogonal views. Later the seed voxel was initialized in gray matter of a segmented image and the growth of tumor (both high and low grade) was observed in serial time steps from three orthogonal views.

This investigation identified a transition point in each case which could be defined as a function of the variable parameters (figure 2 and figure 3).

A more continuous view of the relationship among growth rate, diffusion and transition points can be depicted by figure 4. These results tell us that when diffusion decreases, transition point also decreases and when growth rate decreases, transition increases. Table I shows the estimated parameter values used by Sohana Tanzeem et al. Table II shows the list of transition points that arose in different cases.

Figures 5 through 8 demonstrate the cases where undetectable (t=25 days) and detectable (t=75 days) tumors are shown before and after the transition points respectively.

Table-1: Estimated Parameter Values [4][5]

	High grade glioma	**Low grade glioma**
Doubling Time (days)	28	56
Growth rate, ρ(/day), corresponding to doubling time	0.036	0.018
Linear velocity of the detectable tumor margin in gray matter, v_g (mm/day)	0.046	0.018
Diffusion coefficient in gray matter, D_g (mm^2/day)	0.015	0.005
Linear velocity in white matter, v_w (mm/day)	0.08	0.03
Diffusion coefficient in white matter, D_w (mm^2/day)	0.045	0.015

Table-2: Transition Point (In Days).

	Transition point(days) when seed point is in white matter	Transition point(days) when seed point in gray matter
High grade glioma	36	36
Low grade glioma	55	50

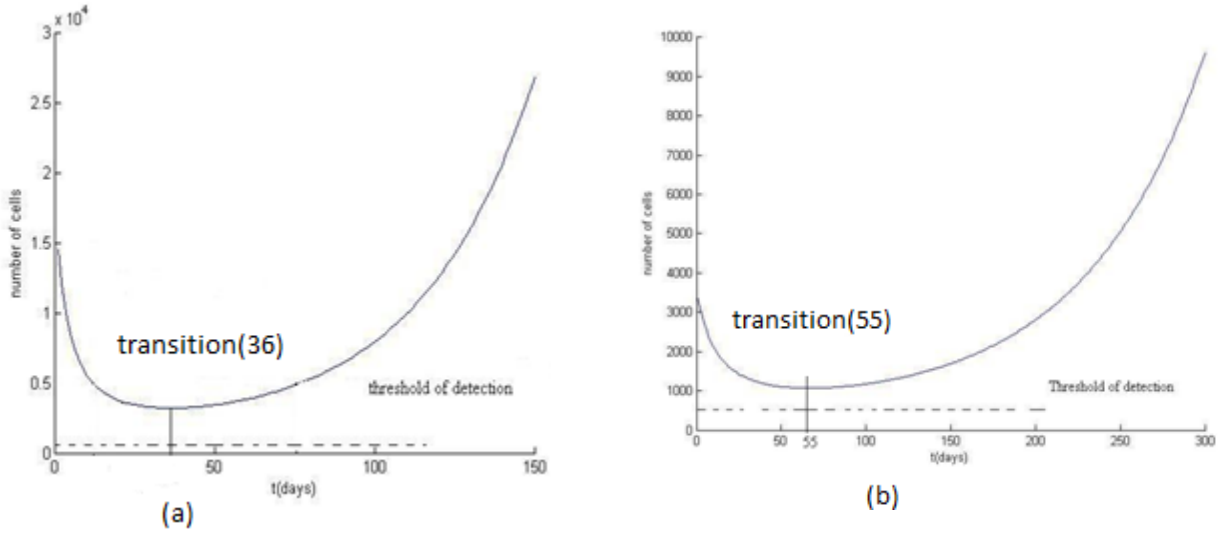


Fig.2: Cell concentration of seed point (in white matter) as a function of time for a) high, b) low grade glioma.

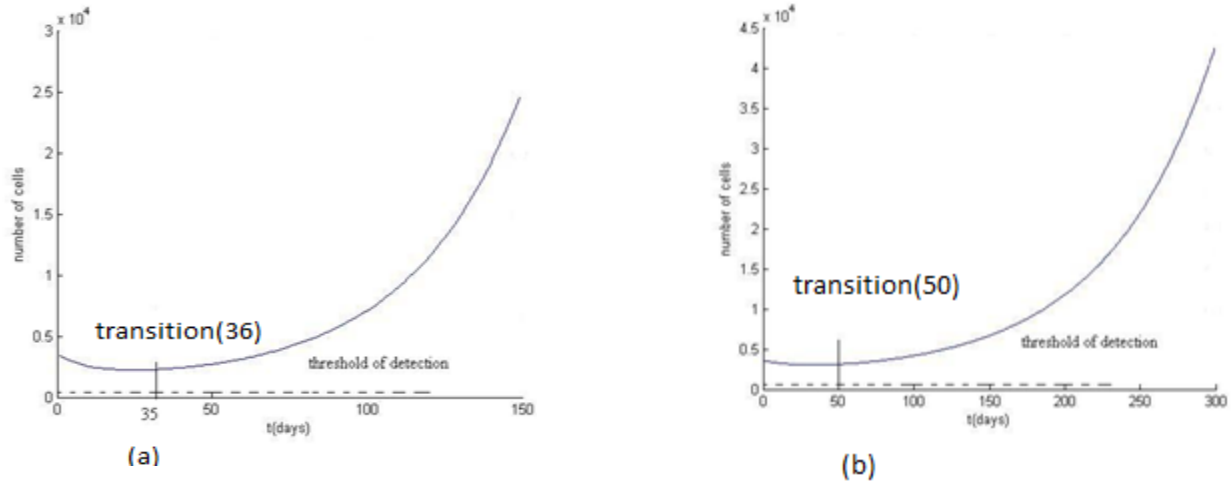


Fig.3: Cell concentration of seed point (in gray matter) as a function of time for a) high, b) low grade glioma.

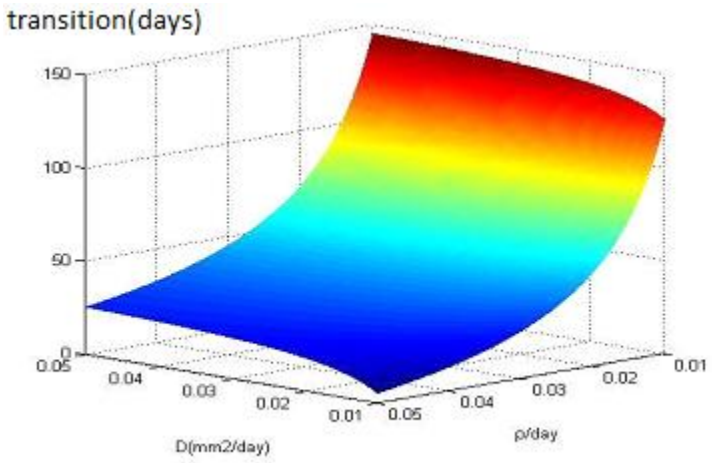
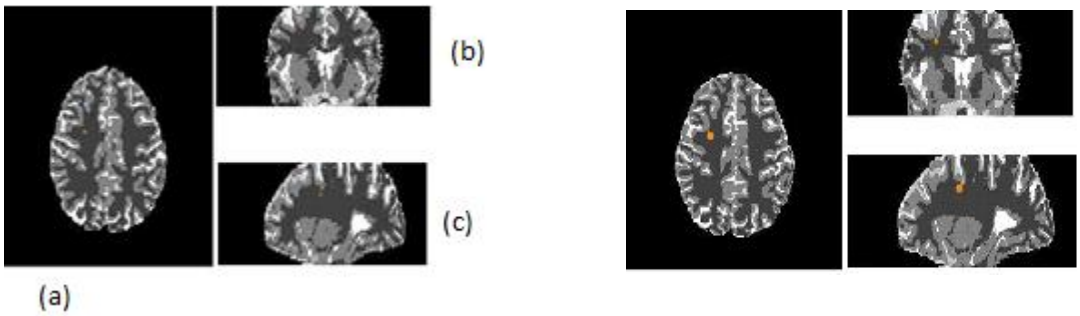
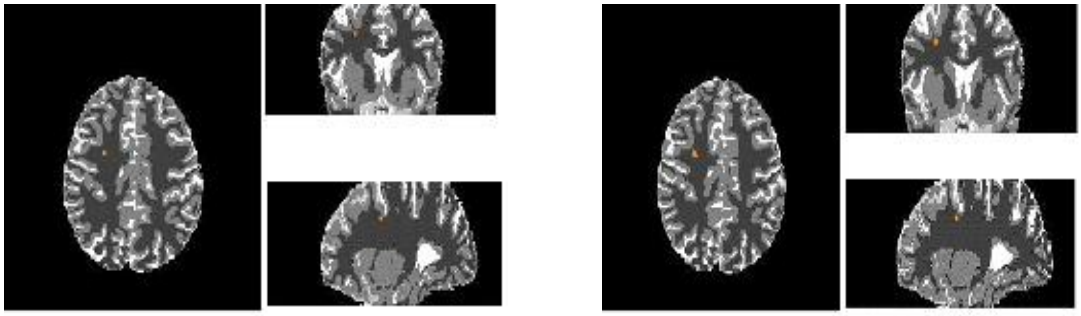


Fig.4: The relationship among proliferation (ρ), Diffusion (D) and transition point.



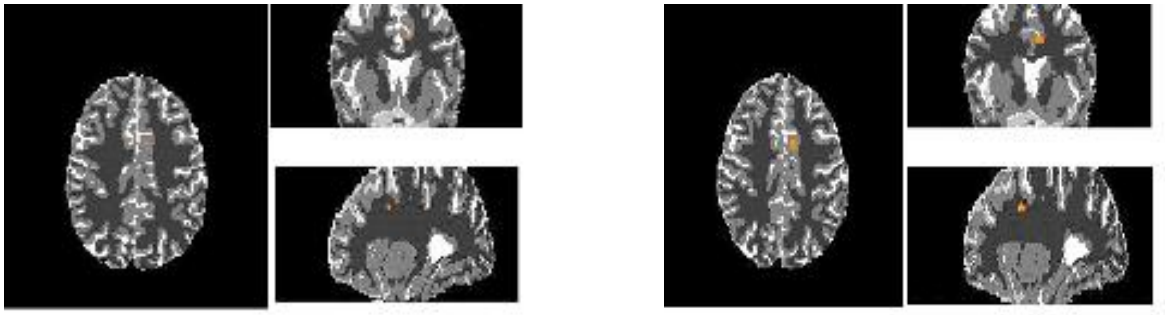
(I) t=25 days (II) t=75 days

Fig.5 (I)-(II): High-grade glioma (ρ=0.036/day, D_w=0.045mm^2/day, D_g=0.015 mm^2/day) from three orthogonal views while seed voxel was initiated in white matter. a) transverse, b) coronal , c) sagittal plane. Transition point is t=36 days.



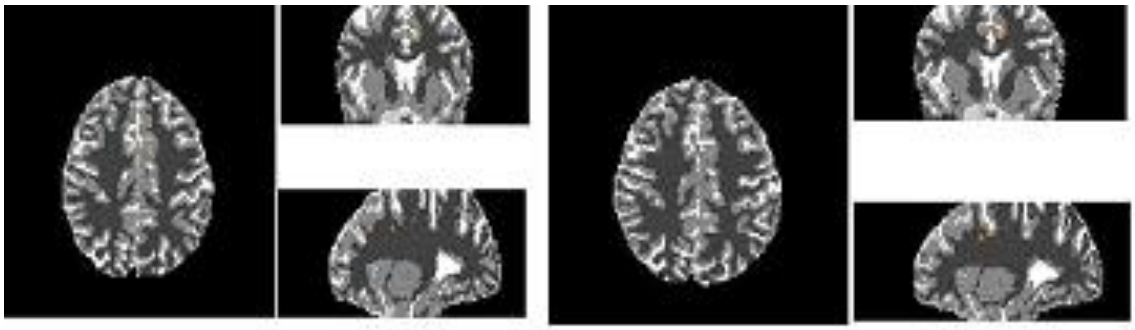
(I) t=25 days (II) t=75 days

Fig.6 (I)-(II): Low-grade glioma (ρ=0.018/day, D_w=0.015mm^2/day, D_g=0.005 mm^2/day) from three orthogonal views while seed voxel was initiated in white matter. Transition point is t=55 days.



(I) t=25 days (II) t=75 days

Fig.7 (I)-(II): High-grade glioma (ρ=0.036/day, D_w=0.045mm^2/day, D_g=0.015 mm^2/day) from three orthogonal views while seed voxel was initiated in gray matter. Transition point is t=36 days.



(I) t=25 days (II) t=75 days

Fig.8 (I)-(II): Low-grade glioma (ρ=0.018/day, D_w=0.015mm^2/day, D_g=0.005 mm^2/day) from three orthogonal views while seed voxel was initiated in gray matter. Transition point is t=50 days.

Discussion

The growth pattern resulted in a transition point in the voxel-wise cell count with respect to time in analysis of Sohana Tanzeem et al.

The transition point occured later in cases of low grade than that of high grade glioma. The existence of the transition point is an inherent characteristic of the form of the model while the temporal shifting of the transition point was a function of the parameter selection. [4][5]

The results found for transition point reflecting the density and spatial diffusion of tumors within the brain are consistent with clinical experience. After gene testing if an abnormality is found regarding cell, that means, if the test indicates that the cell is cancerous (or there is a possibility of existence of cancerous cell in case of family history), the physician may advise the patient to go for a scan. Having the indication of a tumor to be there by gene testing, the tumor still may or may not be detected by scan for diffusion or proliferation being predominant at the phase the scan is done.

Conclusion

Our hypothesis suggests that the phase of a tumor can be reflected by the transition point. Diffusion process is predominant in case of left sided transitional phase of a tumor which makes it undetectable; however, in case of right sided phase, proliferation is predominant and the tumor is detectable in scan. Thus staging depending upon diffusion or proliferation may contribute in treatment plans by gene therapy.

mechanism of actions was not investigated in this study, these could constitute areas of future studies.

Conflict of Interest: The authors do not have any conflict of interest.

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